REPORTS

Antitumor Effects of Doxorubicin in Combination With Anti-epidermal Growth Factor Receptor Monoclonal Antibodies

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Background: A variety of human tumors frequently express high levels of epidermal growth factor (EGF) receptor and its ligand, transforming growth factor α (TGF-α), which in some tumors is associated with poor prognosis. Monoclonal antibodies (MAbs) that block the binding of TGF-α or EGF to the receptor can inhibit proliferation of tumor cells that express the receptor. Studies suggest that these MAbs may enhance the antitumor effects of chemotherapy. *Purpose:* Our purpose was to study, in vitro and in vivo, the antitumor effects of doxorubicin in combination with anti-EGF receptor MAbs against tumor cells expressing high levels of EGF receptor. Our goal was to achieve maximum initial cytoreduction with high-dose doxorubicin in association with prolonged blockade of EGF receptor with MAbs. *Methods:* Anti-EGF receptor MAbs 528 (isotype IgG2a) and 225 (isotype IgG1) were used in combination with doxorubicin against cells from human A431 squamous cell carcinoma and human MDA-468 breast adenocarcinoma. Both A431 and MDA-468 cells express high levels of EGF receptors and TGF-α. Cultured cells were treated with doxorubicin (range, 0-10 n*M*) in the presence or absence of MAb 528 or 225 (range, 0-30 n*M*). At 48 hours, doxorubicin-containing medium was removed, and treatment with antibody was continued for 5 days, when cell proliferation assays were performed. The activity of the agents and the combinations against well-established xenografts in BALB/c nude mice was also studied. In nude mice, doxorubicin was given at doses of 50-100 μg/20 g body weight on 2 successive days, and MAbs 528 and 225 were given at a dose range of 0-2 mg intraperitoneally twice a week. *Results:* MAbs 528 and 225 both enhanced the antitumor effects of doxorubicin against A431 and MDA-468 tumor cells, producing additive growth suppression in cell cultures. MAb 528 increased the antitumor effects of doxorubicin by 32%-42%, and similar results were obtained with MAb 225. In BALB/c athymic mice, the treatment of well-established xenografts with either doxorubicin or anti-EGF receptor MAb alone temporarily inhibited growth, but the combination of both agents substantially enhanced antitumor activity over that of doxorubicin alone in A431 and MDA-468 cell xenografts. The combination treatment of mice bearing A431 xenografts resulted in tumor eradication of 40%-100% in the surviving mice in several independent experiments. The enhanced antitumor activity was dose dependent. *Conclusions:* Our results suggest that anti-EGF receptor MAbs substantially enhance the effects of doxorubicin against well-established xenografts of tumor cells expressing high levels of EGF receptors. *Implications:* Clinical trials with anti-EGF receptor MAbs are being conducted, and trials with anti-EGF receptor MAbs combined with doxorubicin are planned. [J Natl Cancer Inst 85:1327–1333, 1993]

Human epithelial tumors and tumor cell lines frequently express high levels of epidermal growth factor (EGF) receptor and its ligand, transforming growth factor α (TGF-α) (*1*). In some tumors, this expression of high levels of EGF receptor and TGF-α is associated with a more aggressive clinical behavior and poor prognosis (*2-4*). These observations and the fact that the introduction of the TGF-α gene (also known as TGFA) into cells bearing EGF receptors has transforming capacity (*5,6*) suggest that the autocrine pathway constituted by the EGF receptor and TGF-α may have an important role in human tumors.[1]

We have produced monoclonal antibodies (MAbs) that perform the following functions: 1) bind to the EGF receptor with affinity comparable to that of the natural ligand, 2) compete with EGF binding, and 3) block EGF-induced tyrosine kinase activation (*7-10*). When cells that express the EGF receptor, produce its ligand TGF-α, and depend on activation of the EGF receptor for growth are cultured in the presence of saturating concentrations of anti-receptor MAb, binding of TGF-α to the EGF receptor is blocked and ligand-dependent cell proliferation is inhibited (*7,8,11-13*). Treatment with intraperitoneal injections of anti-EGF receptor MAbs results in marked inhibition of tumor growth in mice bearing subcutaneous xenografts of cancer cell lines that express high levels of EGF receptors (*14,15*). However, this treatment does not consistently eliminate xenografts that are well established (*14*). Since the majority of patients with solid tumors that cannot be surgically removed have well-established tumor masses, anti-EGF receptor MAbs alone will probably not be curative in this setting. Therefore, new

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strategies are required to explore the potential clinical applications of these agents.

One such approach is to use combinations of chemotherapeutic agents and anti-EGF receptor MAbs. We consider this a promising strategy for a number of reasons. First, data from culture of cells that depend on EGF receptor activation by endogenous TGF-α for growth demonstrate that, when these cells are cultured at low density, the addition of exogenous growth factor is required for optimal proliferation (*11,16*). Growth of these cells is inhibited by anti-EGF receptor MAbs (*11,16*). By reducing the number of viable tumor cells, chemotherapy may limit the supply of endogenous growth factor in the environment of the remaining tumor cells and thus increase susceptibility to the antitumor effects of anti-EGF receptor MAbs. Second, there is experimental evidence that anti-EGF receptor MAbs may synergize with chemotherapy (*17*). Third, it has been shown recently that both the death of cells exposed to chemotherapy and the death of cells deprived of essential growth factors involve programmed cell death (apoptosis) (*18-21*). These findings suggest the possibility of a common cytotoxic pathway, raising the potential for a combined therapeutic approach. Doxorubicin, an anthracycline antibiotic that has been shown to increase the number of EGF receptors in several cancer cell lines (*22,23*), was the chemotherapeutic agent chosen for the present studies.

Our goal was to analyze, both in vitro and in vivo, the antitumor effects of combined treatment with doxorubicin and anti-EGF receptor MAb against tumor cells expressing high levels of EGF receptor. Our results show a marked tumoricidal effect of this combination, particularly in vivo, where treatment has resulted either in eradication of well-established tumors or in growth inhibition substantially enhanced over that produced by doxorubicin alone.

Materials and Methods

MAbs Against EGF Receptor

Anti-EGF receptor MAbs 528, 225, and 455 were used. MAbs 528 (isotype IgG2a) and 225 (isotype IgG1) bind to the external portion of the EGF receptor with affinity comparable to that of the natural ligand, compete with EGF binding, block EGF-induced tyrosine kinase activation, and inhibit proliferation of cells dependent on EGF receptor activation for growth (*7-9*). MAb 455 (isotype IgG1) binds to the external portion of the EGF receptor, but, unlike MAbs 528 and 225, does not compete with EGF binding, does not block EGF-induced tyrosine kinase activation, and does not inhibit proliferation of cells dependent on EGF receptor activation for growth [(*8*); Baselga J, Masui H, Mendelsohn J, et al.: unpublished observations].

Cell Lines

The human A431 squamous cell carcinoma cell line expresses large quantities of both EGF receptors (2×10^6 per cell) and TGF-α (*7,8*) and is inhibited by MAbs 225 and 528 in culture and in xenografts (*8,9,14*). The human MDA-468 breast carcinoma cell line was obtained from Dr. C. Arteaga at Vanderbilt University (Nashville, Tenn.). Like A431 cells, MDA-468 cells express high levels of EGF receptors (10^6 per cell) and TGF-α and is inhibited by MAbs 225 and 528 in culture and in xenografts (*15*). Both cell lines were grown at 37 °C in monolayer culture with Dulbecco's Modified Eagle medium (DMEM) and Ham's medium F-12 (1:1) containing 10% fetal bovine serum.

Cell Culture and Growth Assay

Cells were seeded in 12-well plates (Corning Glass Works, Corning, N.Y.) at a density of 5000 cells per well. On the following day, cells were treated with varying concentrations of doxorubicin (range, 0-10 n*M*) (Adria Laboratories, Columbus, Ohio) either in the presence or in the absence of MAb 528, 225, or 455 at different concentrations (range, 0-30 n*M*). At 48 hours, doxorubicin-containing medium was removed, cells were washed twice by addition and decantation of phosphate-buffered saline (PBS) (pH 7.4), and the treatment with antibody was continued as before. On day 5, the cells were counted after trypsinization using a cell counter (Coulter Electronics Inc., Hialeah, Fla.).

Assay of Tumor Growth in Athymic Mice

BALB/c athymic mice, 6-8 weeks of age, were used. These mice were bred and maintained in accordance with institutional guidelines at the Memorial Sloan-Kettering Cancer Center animal facility as described previously (*24*). Cultured A431 and MDA-468 cells were trypsinized and washed with serum-free DMEM and Ham's medium F-12 (1:1). Cells (10^7) were injected subcutaneously into animals on day 0. MDA-468 cells were injected only into female mice. Tumor size was measured twice a week using the formula $\pi/6 \times$ larger diameter $\times$ (smaller diameter)^2. Animals were considered to be free of tumor if no tumor could be detected in two successive tumor evaluations.

When tumors reached a mean size of greater than 0.3 cm^3 (A431 cells) or greater than 0.2 cm^3 (MDA-468 cells), animals were divided into different treatment groups. Each animal experiment included four treatment groups: control, doxorubicin alone, antibody alone, and doxorubicin in combination with antibody. Each treatment group consisted of at least five animals with comparable tumor size among groups from the same experiments, so that initial tumor size was not a variable within a particular experiment. Doxorubicin was given intraperitoneally in 0.5 mL distilled water at a dose range of 0-100 µg/20 g body weight for 2 successive days. MAb 528, MAb 225, or nonspecific polyclonal mouse IgG antibody (Sigma Chemical Co., St. Louis, Mo.) was given intraperitoneally in 0.5 mL of phosphate-buffered saline (PBS) (pH 7.4), with a dose range of 0-2 mg. Antibody treatment was administered twice weekly, a schedule that has previously been shown to maintain stable receptor-saturating blood levels at doses of 1 mg or more per injection (*14*). Control animals were treated with 0.5 mL of PBS twice a week.

Finally, groups of at least five mice were treated with a combination of doxorubicin and either MAb 528, MAb 225, or polyclonal mouse IgG antibody at the same dose levels and treatment intervals as described above for each separate treatment.

Results

Treatment of A431 and MDA-468 Cells in Culture

Culture of A431 or MDA-468 cells with doxorubicin at increasing concentrations (0-10 n*M*) for 2 days resulted in a dose-dependent inhibition of growth assayed on day 5 of culture. Treatment with either MAb 528 or MAb 225 (0-30 n*M*) continuously for 5 days produced a dose-dependent inhibition of growth of both cell lines. The combined treatment with increasing concentrations of doxorubicin and anti-EGF receptor MAb 528 resulted in an additive inhibition of growth in both A431 cells and MDA-468 cells increasing the inhibitory effects of doxorubicin by 32%-42% (Fig. 1). Similar results were obtained when doxorubicin was used in combination with anti-EGF receptor MAb 225 against both cell lines (data not shown). The increased antitumor activity was not observed when cells were treated with doxorubicin in combination with the non-blocking anti-EGF receptor MAb 455 (data not shown).

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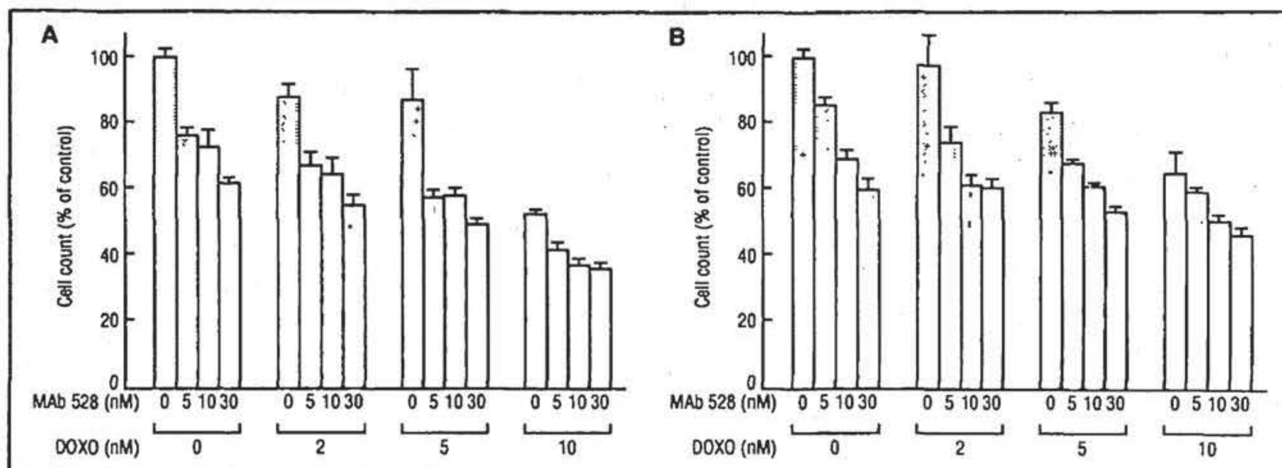

Fig. 1. Inhibitory effects of doxorubicin in combination with MAb 528 in cultures of A431 cells (A) and MDA-468 cells (B). Doxorubicin was added to cultures at increasing concentrations (0-10 *nM*) for 2 days. MAb 528 was present at described concentrations for 5 days. Cell number was determined on day 5 using a cell counter. Results represent the mean ± SE of triplicate readings.

Treatment of A431 Cell Xenografts

We explored the in vivo effects of the combination therapy in a series of experiments. First, doxorubicin administered at 100 μg/20 g body weight intraperitoneally on 2 successive days was determined to be an LD_{10}, that is, a dose killing 10% of mice. Our initial pilot study of combination therapy used a limited number of mice bearing well-established A431 xenografts more than 0.4 cm^3 in size. When animals, in groups of at least five, were treated with either MAb 528 alone (1 mg twice a week for 2 weeks) or doxorubicin alone (100 μg/20 g body weight for 2 days), tumor growth rate was modestly inhibited by less than 50% at 15 days (data not shown). However, treatment of eight animals with the combination of MAb 528 and doxorubicin, at the same dose and schedule, resulted in complete eradication of tumors in all five animals (100%) that were alive at 15 days. After the 15 days of follow-up, the animals in this group were killed, and lack of residual tumor was confirmed by necropsy.

We conducted experiments to confirm the antitumor activity of doxorubicin and MAb 528 in larger numbers of athymic mice bearing well-established subcutaneous xenografts of A431 cells. When tumors reached a mean size of 0.4 cm^3, the mice were allocated into groups with comparable tumor sizes, and therapy with the above regimen was started (Fig. 2, A). In untreated animals, tumors grew rapidly and all of the animals died within 5 weeks, as expected. Doxorubicin alone initially slowed tumor growth, but within 10 days tumors began to regrow rapidly. Treatment with MAb 528 reduced tumor growth rate; however, as expected from previous studies with well-established tumors (*14*), the xenografts were not eliminated. In contrast, the combination treatment with doxorubicin and MAb 528 resulted in a major antitumor effect (Fig. 2, A).

We performed a total of three independent experiments (the pilot study above plus the experiments shown in Fig. 2, A and B) to determine in A431 cell xenografts the antitumor activity of a combination of doxorubicin, 100 μg/20 g weight given on 2 successive days and 1 mg MAb 528 given twice a week. The data from these experiments have been pooled in Table 1. A total of 26 animals were treated with the combination therapy. After 15 days of treatment, 21 animals (81%) were alive. Eighteen of these mice were free of tumor by day 15, and the other three had no tumors by day 30. Therefore, by day 30, all 21 surviving animals in the combination group (100%) had their tumors eradicated. After 100 days from the start of treatment, only two of the 16 surviving animals treated with the combined therapy had tumors, which were regrowing slowly.

To demonstrate that the antitumor effects of the combination were not due to a nonspecific action of mouse IgG given in combination with doxorubicin, we treated mice bearing comparable A431 xenografts with doxorubicin in combination with a nonspecific mouse IgG. We used the same dose and schedule as with MAb 528. There were no differences in mean tumor size between animals treated with doxorubicin alone or in combination with mouse IgG (Fig. 2, B).

Additional experiments were designed to determine the dose dependency of the response to combination therapy. Our previous pharmacologic studies indicated that an MAb treatment schedule of 1 mg given intraperitoneally twice weekly would produce stable blood levels of antireceptor MAb capable of saturating xenograft EGF receptors (more than 10 times the equilibrium dissociation constant, K_d) (*14*). The results observed with MAb 528, given alone or in combination with doxorubicin and at a higher dose (2 mg intraperitoneally), twice a week for 5 weeks on a schedule similar to the experiment in Fig. 2, A, were comparable to those observed with the 1-mg dose (Table 1). When xenografts were treated with combination therapy utilizing MAb doses of less than 1 mg,

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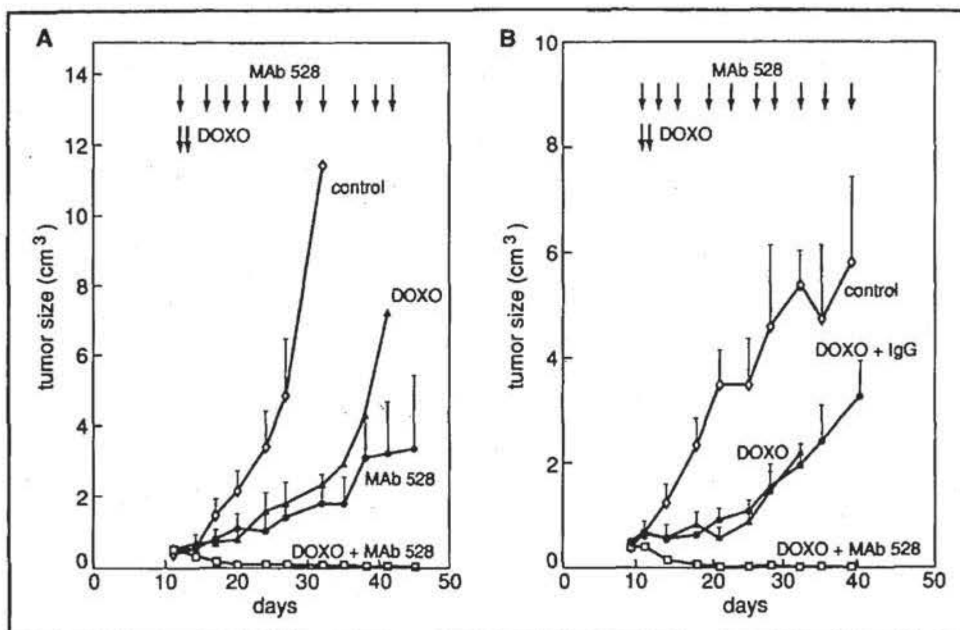

Fig. 2. Antitumor activity of MAb 528 in combination with doxorubicin (DOXO) on well-established A431 squamous cell carcinoma xenografts in athymic mice. Treatment was started when tumors reached a mean size of 0.4 cm^3 on day 11 in Fig. 2, A or day 9 in Fig. 2, B. Each treatment group consisted of at least five animals. A total of 10 mice were treated in the combination group in the experiment plotted in Fig. 2, A, and 8 animals in Fig. 2, B. Results are given in mean tumor size ± SE. Error bars are not present when less than three animals remained alive in a certain treatment group. Doxorubicin (100 µg/20 g body weight) was given intraperitoneally on days 1 and 2 of treatment (day 11 and 12 or day 9 and 10 after tumor cell inoculation). MAb 528 (1 mg) was given intraperitoneally on day 1 of treatment and twice a week thereafter for a total of 10 doses. A) Treatment with either doxorubicin alone or MAb alone partially inhibited tumor growth. Doxorubicin in combination with MAb 528 completely eradicated all tumors in the animals surviving on day 30 (N = 8). B) Doxorubicin in combination with a nonspecific mouse IgG did not result in a greater antitumor effect than doxorubicin alone, while doxorubicin in combination with MAb 528 resulted in disappearance of all tumors in the animals surviving on day 30 (N = 6). Arrows show days on which treatment was administered.

the antitumor effects were reduced (data not shown). This result suggests that saturation of EGF receptors may be required to achieve optimal results with doxorubicin plus anti-EGF receptor blockade therapy. We also tested the antitumor response to the combination therapy with a lower dose of doxorubicin (50 µg given intraperitoneally on 2 successive days). Doxorubicin treatment alone had no effect, but combination therapy with doxorubicin and MAb 528 was again seen to have a strong inhibitory effect. However, in contrast to the results with higher doses of doxorubicin, no tumor xenografts were completely eradicated (data not shown).

The above experiments were performed with MAb 528 IgG2a, which has the capacity to activate complement-mediated cytotoxicity as well as cell-mediated toxicity (*25*). We decided to repeat the treatment protocols with MAb 225 IgG1, which bears an Fc portion that is immunologically nonreactive and has been shown in earlier studies to be unable to mediate toxicity via the complement or cellular immune pathways (*25*). Again, strong anticancer effects were observed with combined therapy; tumors were eradicated in four of the 10 animals (40%) surviving on day 15 after treatment (Fig. 3, A; Table 1). When doxorubicin was administered at a 50% reduced dose (50 µg/20 g body weight on 2 successive days) in combination with MAb 225 (1 mg intraperitoneally twice a week), results similar to those obtained with reduced-dose doxorubicin and MAb 528 were observed (data not shown).

Table 1. Eradication of tumors by high-dose doxorubicin and anti-EGF receptor MAbs*

Treatment†	Initial No. of mice	Mice alive on day 15		Mice tumor-free on day 15	
		No.	%	No.	%
None	31	27	87	1	3
Doxorubicin	29	23	79	1	3
Doxorubicin + 1 mg IgG	9	6	67	0	0
1 mg MAb 528	12	12	100	1	8
Doxorubicin + 1 mg MAb 528	26‡	21	81	18§	69
2 mg MAb 528	6	6	100	0	0
Doxorubicin + 2 mg MAb 528	6	6	100	4	67
1 mg MAb 225	10	10	100	2	20
Doxorubicin + 1 mg MAb 225	10	10	100	4	40

*Well-established (6-12 days) A431 xenografts were treated with doxorubicin, MAb, or combination therapy. The status of animals and xenografts 15 days after the initiation of treatment is shown. Results of five experiments are given. Data on animals that received the same treatment and dose have been pooled.

†Doxorubicin was given intraperitoneally at 100 µg/20 g twice weekly. MAb or IgG was administered intraperitoneally twice weekly at the stated doses.

‡Animals from the pilot study and experiments shown in Fig. 2, A and B, are included.

§The remaining three animals alive with tumors on day 15 had no tumors by day 30.

Treatment of MDA-468 Cell Xenografts

We also examined the effects of combination therapy on MDA-468 breast adenocarcinoma cells in nude

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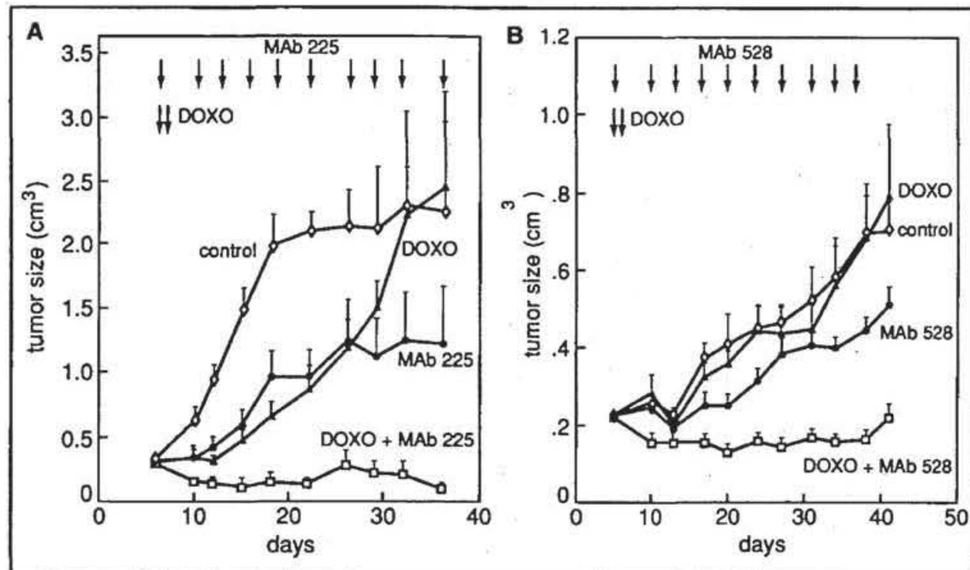

Fig. 3. A) Antitumor activity of MAb 225 in combination with doxorubicin (DOXO) on well-established A431 squamous cell carcinoma xenografts. Treatment was started when tumors reached a mean size of 0.3 cm^3. A total of 10 mice were treated in the combination group. Results are given in mean tumor size ± SE. Doxorubicin (100 μg/20 g body weight) was given intraperitoneally on days 1 and 2. MAb 225 (1 mg) was given intraperitoneally on day 1 and twice a week thereafter for a total of 10 doses. Treatment with either doxorubicin alone or MAb alone resulted in transient inhibition of tumor growth. Doxorubicin in combination with MAb 225 had a pronounced antitumor activity. Arrows show days on which treatment was administered. B) Antitumor activity of MAb 528 in combination with doxorubicin (DOXO) on well-established MDA-468 breast adenocarcinoma xenografts. Treatment was started when tumors reached a mean size of 0.2 cm^3. A total of 9 mice were treated in the combination group. Results are given in mean tumor size ± SE. Doxorubicin (100 μg/20 g body weight) was given intraperitoneally on days 1 and 2. MAb 528 (2 mg) was given intraperitoneally on day 1 and twice a week thereafter for a total of 10 doses. Treatment with either doxorubicin alone or MAb alone resulted in transient inhibition of tumor growth. Doxorubicin in combination with MAb 528 confirmed the antitumor activity observed in A431 cells. Arrows show days on which treatment was administered.

mouse xenografts. To treat animals, we used the same schedule as in the experiment showed in Fig. 1, A, except that the dose of MAb 528 was 2 mg given intraperitoneally twice weekly based on our previous studies with this cell line (*15*). Doxorubicin alone at the maximally tolerated dose (100 μg/20 g body weight on 2 successive days) did not have a noticeable antitumor activity, and treatment of these established tumors with MAb 528 only slowed tumor growth, which was predicted on the basis of our previous studies (*15*). In mice bearing MDA-468 xenografts, combination therapy with doxorubicin and MAb confirmed the antitumor activity observed in A431 xenografts (Fig. 3, B). One of nine (11%) treated mice surviving on day 30 was tumor free.

In summary, our studies in mice demonstrate that the treatment of well-established A431 cell and MDA-468 cell xenografts with a high dose of doxorubicin (100 μg/ 20 g weight on 2 successive days) in combination with either MAb 528 or 225 at a dose of 1 mg twice a week, or higher, results in a major antitumor effect. The results were most impressive in our A431 cell xenograft model, where the combination treatment resulted in eradication of 40% to 100% of the tumors in surviving animals in 5 experiments. Lower doses of doxorubicin or antibody in combination were less effective.

Discussion

These studies demonstrate that anti-EGF receptor MAbs are capable of enhancing the effects of doxorubicin against well-established xenografts of a squamous cell carcinoma line and an adenocarcinoma that express high levels of EGF receptor. Based on considerations presented earlier in the report, our goal was to achieve a maximum initial cytoreduction by chemotherapy in association with a complete receptor blockade. Therefore, our in vivo experiments were designed to give a high-dose intensity of doxorubicin accompanied by a prolonged blockade of EGF receptors with MAbs. We observed comparable results in multiple, independently conducted experiments, employing two different anti-EGF receptor MAbs with distinct isotypes and tumors with two different histologic types. The inhibition was dose dependent for both doxorubicin and MAb.

Two studies (*17,26*) have shown that combination treatment with the chemotherapeutic agent cisplatin and antigrowth factor receptor MAb inhibited tumor xenograft growth in nude mice. Our studies demonstrate, however, for the first time that treatment of well-established tumors with the combination of antireceptor therapy and a chemotherapeutic agent has resulted in tumor-free animals, as assessed either by a necropsy examination or by a 100-day follow-up period.

Our results lead us to question the mechanism that causes the marked antitumor effects of chemotherapeutic agents when used in combination with antigrowth factor receptor MAbs. Doxorubicin has been shown to increase EGF receptor expression in some cell lines (*22,23*). In experiments not presented here, we found that doxorubicin administered to A431 cells in noncytocidal concentrations increased the levels of EGF receptor and TGF-α messenger RNA by more than threefold within hours, followed by a 2.6-fold increase in EGF receptor number and a 2.4-fold increase in the amount of TGF-α released into the conditioned culture medium (*27*). These results, together with the strong antitumor activity of combined therapy, led us to entertain the hypothesis that, in cells recovering from noncytocidal

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